

## Acquired heart disease in low-income and middle-income countries

Curry, C., Zuhlke, L., Mocumbi, A., & Kennedy, N. (2017). Acquired heart disease in low-income and middle-income countries. *Archives of Disease in Childhood*, 1-5. <https://doi.org/10.1136/archdischild-2016-312521>

**Published in:**  
Archives of Disease in Childhood

**Document Version:**  
Peer reviewed version

**Queen's University Belfast - Research Portal:**  
[Link to publication record in Queen's University Belfast Research Portal](#)

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## Acquired heart disease in Low and Middle Income Countries

### Introduction

In low and middle-income countries (LMIC) the child health focus has typically been on the high burden of communicable diseases. While implementation of the millennium development goals has seen the under-five mortality decline by more than half between 1990 and 2015, further reductions require more focus on neglected and non-communicable diseases<sup>1</sup>. In recent years there has been increasing interest in the burden associated with congenital and acquired heart disease.

There are little reliable data concerning the spectrum and prevalence of paediatric cardiac disease in LMIC, but enough to know that the burden is considerable with patients typically presenting with advanced disease<sup>2</sup>. A small number of studies have characterised the spectrum of acquired heart disease in specific populations in LMIC. One study in Malawi found that acquired heart disease accounted for 44.4% of pathology presenting to an urban paediatric cardiology clinic, predominantly rheumatic heart disease and dilated cardiomyopathy<sup>3</sup>. Multiple studies have confirmed RHD as the leading cause of heart disease in children in developing countries<sup>4</sup>. **Indeed, the burden of disease is significant in comparison with other better studied and funded diseases in LMIC. For example 314,000 people die per annum with RHD, which is similar to the number of deaths due to neonatal sepsis (351,000) or as a result of congenital heart disease (303,000)<sup>5</sup>. It has been estimated that RHD has a mortality about 50% of malaria, yet receives only 0.07% of global health funding<sup>6</sup>.**

Studies In endemic parts of Africa and Asia have shown that HIV and TB are a significant cause of childhood cardiac disease while endomyocardial fibrosis is important in specific, high prevalence areas of Africa, Asia and South America<sup>7,8</sup>.

In this review, therefore, we will concentrate on the significant causes of acquired heart disease in children in LMIC; rheumatic heart disease, tropical endomyocardial fibrosis, dilated cardiomyopathy (including HIV) and tuberculous pericarditis.

### Rheumatic Heart Disease

While rheumatic heart disease (RHD) ceased to be a public health concern in most developed countries decades ago, it remains the largest cardiac cause of morbidity and mortality in children, adolescents and young adults in LMIC worldwide. Most recent figures estimate that there are nearly 33 million people with rheumatic heart disease globally, accounting for around 275, 000 deaths per year<sup>9</sup>. A recent systematic review and meta-analysis of population based studies across Oceania, Asia, Africa, Latin America and Europe found evidence of clinically manifest disease in 2.7 per 1000 children and clinically silent disease in 21 per 1000 children in endemic countries<sup>10</sup>.

The development of RHD is associated with severe or multiple episodes of acute rheumatic fever (ARF) which peak between the ages of five and fourteen<sup>11</sup>. Group A streptococcal infection of the pharynx leads to an autoimmune response characterized by various combinations of fever, joint pain and swelling, carditis, chorea and skin manifestations. Clinical diagnosis is guided by the Jones criteria, updated in 2015, and **streptococcal serology which is often not available in LMIC**<sup>11</sup>. The development of chronic cardiac complications is highly preventable with the use of antibiotics as primary and secondary prophylaxis<sup>11</sup>. Without effective treatment of repeated episodes, the development of cross-reactive immune complexes and inflammation of the heart valves and myocardium results in permanent valvular damage and the development of RHD (Figure 1). Valvular manifestations are typically mitral and/or aortic regurgitation with stenosis in long-standing cases, leading to the development of cardiac failure and increased risk of embolic stroke, endocarditis and atrial fibrillation<sup>11</sup>. Barriers to the implementation of primary and secondary prevention can include limited access to primary care, lack of healthcare workers, expense of microbiological diagnosis or echocardiography, poor community awareness and lack of recognition of ARF by clinicians. For example, in one cohort study of 309 newly diagnosed patients with RHD in Uganda none had a confirmed history or ARF<sup>12</sup>.

Successful management of RHD hinges on secondary penicillin prophylaxis to prevent disease progression, specialist review and serial cardiac imaging, appropriate prescription and monitoring of

anticoagulation and timely referral for cardiac surgery<sup>11</sup>. Unfortunately, in many LMIC access to these services is poor and many patients present late in the disease course with established RHD, advanced cardiac failure, embolic stroke, infective endocarditis or symptomatic arrhythmias<sup>11</sup>. The REMEDY study, an international hospital based registry of 3,343 patients with symptomatic RHD in 12 African countries, India and Yemen, has highlighted the ongoing challenges in the management of RHD in LMIC<sup>9,13</sup>. Only 54.8% of patients were on secondary penicillin prophylaxis. Appropriate use of oral anticoagulation was variable, with low rates even amongst patients with mitral stenosis or established left atrial thrombus. Monitoring of warfarin prescription provided challenges, with 12.2% having no INR monitoring and 34% monitored less than 3 times in 6 months. Only 10.3% of patients requiring surgery or percutaneous procedures received intervention, most of whom were in upper-middle-income countries<sup>9</sup>. At two year follow up 16.9% of the cohort had died at a median age of 28.7<sup>9</sup>.

**Earlier detection and management of ARF and RHD in LMIC is clearly critical to reducing the burden of disease.** Multiple studies using portable echocardiography in school-aged children have detected a high prevalence of latent, pre-clinical disease, raising the possibility of successful secondary prophylaxis in these children before complications occur<sup>11</sup>. One study in Fiji showed that nurse led echocardiographic screening had good sensitivity and specificity in detecting mitral regurgitation in RHD<sup>14</sup>. However it remains unclear which children with latent disease will benefit from prophylaxis as a proportion of those with borderline disease improve to normal after medium-term follow-up<sup>15</sup>. **Further large-scale trials are required before recommending the implementation of a potentially very costly and skill intensive intervention.** Targeted screening of index cases may be a useful approach to identify those at risk of developing symptomatic disease<sup>16</sup>.

**The findings of REMEDY reinforce the fact that RHD is a disease of poverty and social injustice. Those affected are predominantly young, largely unemployed and two thirds are female<sup>9</sup>.** It is known that household overcrowding, rural location and under-nutrition are all associated with

increased risk of ARF and RHD<sup>11</sup>. Education beyond primary school is associated with significantly decreased risk of mortality<sup>9</sup>. Encouragingly there has been a renewed interest in tackling RHD in recent years, with the World Heart Federation calling for a 25% reduction in premature mortality from RHD by 2025 and the Social Cluster of the Africa Union Commission laying out key priorities for tackling RHD in 2015<sup>17</sup>. Central to these efforts will be development of robust surveillance programmes for RHD, increased access to primary and secondary prophylaxis and the establishment of cardiac surgical services in LMIC. **Improvement of the social determinants of health in LMIC, by tackling living conditions and overcrowding, is an over-riding challenge in countries with high prevalence of RHD.**

**After many years of research there is renewed hope of the development of an effective group A streptococcal vaccine to aid primary prevention of RHD.** Challenges in development have included the plethora of group A streptococcal strains, the risk of immune reactivity to the vaccine and commercial viability<sup>18</sup>.

### **Tropical endomyocardial fibrosis**

Endomyocardial fibrosis (EMF) is the most common cause of restrictive cardiomyopathy worldwide, characterised by deposition of fibrous tissue in the endomyocardium<sup>19</sup>. This neglected disease typically affects poor, rural populations in tropical LMIC, with geographically distinct pockets of high prevalence in Africa, Asia and South America. In contrast to rheumatic heart disease, the main challenges in managing EMF are a lack of knowledge of the origin and pathogenesis of the disease with no specific treatment or evidence based prevention strategies currently available<sup>19</sup>.

Although first described in 1948, the pathogenesis of the disease remains unclear. Proposed, but unproven disease mechanisms include hypereosinophilia, infection, autoimmune, genetic, dietary and geochemical factors<sup>19</sup>. The occurrence of EMF in small numbers of people from Europe and North America after short stays in endemic regions supports the role of an infectious or other environmental cause, however no specific trigger has been identified<sup>19</sup>. Familial occurrence and high

incidence among certain ethnic groups has indicated a genetic susceptibility to the disease<sup>19</sup>.

Critically, EMF cannot be explained by a single cause in all areas where it has been reported. It is likely to be triggered by multiple independent environmental factors acting on individuals with a genetic predisposition<sup>19</sup>.

An estimated 10 million people are affected by EMF worldwide although geographic distribution in affected countries is not uniform<sup>20</sup>. In endemic areas of Africa EMF is the second most common cause of admission for acquired heart disease (after rheumatic heart disease) and accounts for 20% of all cases of heart failure<sup>21</sup>. **Few systematic studies of prevalence in the community exist, but a community based study in a rural area of Mozambique using portable echocardiography found evidence of EMF in 19.8% of the general population, and 28.1% of those aged 10-19 years<sup>22</sup>.**

Children and adolescents are predominantly affected, with over half of cases seen in the first decade of life<sup>21</sup>.

If recognised, the initial clinical features of EMF are a febrile illness associated with pericarditis and eosinophilia, dyspnoea, itching and periorbital swelling<sup>19</sup>. This is followed by ventricular thrombosis affecting usually the apices and subvalvular apparatus which evolves to form endocardial fibrosis typical of the advanced stage of the disease. The resulting impedance of ventricular filling and valve distortion leads to restrictive physiology with atrioventricular regurgitation, and the typical appearance of small ventricles with severely dilated atria (Figure 2). Echocardiography is the mainstay of diagnosis<sup>8</sup>. The majority of patients present late with features of longstanding cardiac failure, clubbing, growth retardation, testicular atrophy, pubertal delay and cachexia. Marked ascites out of proportion to peripheral oedema is typical, leading some authors to hypothesise EMF to be a systemic syndrome with associated peritoneal inflammation<sup>19</sup>. Atrial fibrillation occurs in greater than 30% of cases, and other conduction abnormalities are common<sup>19</sup>.

No specific treatment has been developed to treat EMF. Medical management is based on the symptomatic treatment of heart failure, arrhythmias and anticoagulation where indicated<sup>19</sup>. Short

courses of steroids have been used to suppress eosinophilia in the acute phase of the disease, although there is a lack of evidence to support their use<sup>19</sup>. Surgical intervention has been shown to improve symptoms and improve survival in EMF, most commonly using targeted endocardial resection combined with valve repair or replacement<sup>23</sup>. **However, access to cardiac surgery in endemic regions is extremely limited, with only a handful of sub-Saharan African countries having independent cardiac surgery programmes<sup>24</sup>.** Research into surgical intervention is limited to a small number of studies in patients with advanced disease<sup>21</sup>.

The prognosis of EMF remains extremely poor, with 75% of patients dying within 2 years of diagnosis<sup>19</sup>. Death is typically due to progressive heart failure, pulmonary embolism or fatal ventricular arrhythmia<sup>21</sup>. There is an urgent need for further research into the aetiology and mechanisms of the disease in order to develop effective treatment and prevention strategies.

### **Dilated Cardiomyopathy**

In developed countries dilated cardiomyopathies (DCM) account for about half of all childhood heart transplants and population cohort studies have found an annual incidence of cardiomyopathy of up to 1.24 per 100,000 children under the age of ten<sup>25</sup>. Epidemiological data is lacking in developing countries, but the disease burden is thought to be significant given the association of cardiomyopathies with malnutrition and infectious disease<sup>26</sup>. One tertiary centre in Nigeria recorded cardiomyopathy in nearly 3% of children accessing cardiac services in South-west Nigeria<sup>27</sup>. A lack of specialist investigations poses significant problems to the diagnosis and management of paediatric DCM in LMIC. The cause in most children is not known.

HIV associated cardiomyopathy is an important known cause. The Heart of Soweto study found that HIV associated DCM was the most common cardiac diagnosis amongst HIV positive patients<sup>28</sup>. In one Ugandan study, cardiac abnormalities were present in 50% of newly diagnosed HIV positive children<sup>29</sup>. Direct infection of myocytes with HIV triggering an autoimmune response is thought to underlie HIV cardiomyopathy, although nutritional deficiencies, and opportunistic infections are also

implicated<sup>29</sup>. HIV cardiomyopathy is an indication to start anti-retroviral therapy, independent of CD4 count, and there is justification for routine echocardiography in HIV-positive children in order to identify pre-symptomatic cardiac disease. However in areas where early antiretroviral treatment is available, the incidence is falling.

In Latin America, Chagas disease caused by *Trypanosoma cruzi* is known to be a significant infective cause of DCM. Although usually observed in chronic disease 10-20 years after initial infection, a recent epidemiological study of more than 3000 children in Mexico identified 14 children with pre-symptomatic chagasic cardiomyopathy<sup>30</sup>. It is unclear if antiparasitic treatment improves the prognosis once the disease has developed<sup>31</sup>.

**$\beta$  thalassemia is a common inherited blood disorder in the Indian sub-continent, south-east and central Asia, Southern China, Mediterranean, North Africa and the Middle East, characterised by severe anaemia requiring regular blood transfusions<sup>32</sup>. These children are at risk of Iron-overload related cardiomyopathy in LMIC. A public health review in 2008 estimated over 25000 annual births of transfusion dependent thalassemia worldwide, mostly in LMIC<sup>33</sup>. While only 11.7% of children who require transfusions receive them, those who do carry a significant risk of developing cardiac iron overload and cardiomyopathy with a subsequent rapid decrease in myocardial function and death<sup>33</sup>. This has been demonstrated in children under the age of 10 despite receiving chelation therapy<sup>34</sup>. The high cost of managing these patients presents a difficult challenge to health systems in LMIC.**

### **Tuberculous Pericarditis**

WHO figures in 2015 estimated that globally, 1 million children are infected with TB, predominantly in LMIC in Asia and Sub-Saharan Africa, accounting for more than 136,000 deaths each year<sup>35</sup>. TB is one of the most common causes of pericardial effusion in TB endemic countries, with approximately



1-4% of children with TB developing pericarditis<sup>36</sup>. The HIV pandemic has dramatically changed the epidemiology, manifestation and treatment options for TB pericarditis. In one large study in South Africa, 83% of patients aged 15-29 undergoing pericardiocentesis for large pericardial effusions had TB, with over 50% of patients co-infected with HIV<sup>37</sup>. HIV predisposes patients to more disseminated disease, with increased risk of pericardial and myocardial involvement<sup>37,38</sup>.

In children, TB pericardial disease has three main presentations: pericardial effusion (most common), constrictive pericarditis, and a combination known as effusive-constrictive disease. Most frequently, the pericardium is infiltrated from an infected contiguous subcarinal lymph node<sup>38</sup>. Once in the pericardium, an inflammatory process with granuloma formation results in the production of a fibrinous exudate<sup>37</sup>.

Importantly, the clinical presentation is variable and often non-specific. However, given the poor availability and sensitivity of microbiological diagnosis in LMIC, the diagnosis is usually based on clinical signs alone. A high index of suspicion is required in endemic areas<sup>39</sup>. Children typically present with signs and symptoms of heart failure, including persistent cough, dyspnoea, chest pain and hepatomegaly in addition to fever, night sweats and failure to thrive<sup>38</sup>. Chest radiography may show cardiomegaly with a globular silhouette, while echocardiography can confirm the presence of effusions, often associated with fibrinous threads and a “bread and butter” appearance of the visceral pericardium and may identify associated mediastinal lymphadenopathy<sup>38</sup>. **Valvular disease is not a typical feature of TB pericarditis however the myocardium is often affected adding to the complexity of the disease. The following features of pericardial fluid suggest TB: a predominantly lymphocytic cell count, elevated protein and LDH level and glucose 3.0–5.5 mmol/L are suggestive but not diagnostic of TB<sup>38</sup>.**

Specific research in the management of childhood tuberculous pericarditis is lacking, and adult management regimens are followed<sup>40</sup>. A typical approach is pericardiocentesis if there is evidence of tamponade, followed by an initial regimen of rifampicin, isoniazid, pyrazinamide and ethambutol

for at least two months followed by isoniazid and rifampicin for a further four months. Pericardial **TB management in children is complicated by the lack of suitable formulations of medications for the first years of life.** The multicentre IMPI trial showed that the use of adjunctive high dose steroids reduced the incidence of constrictive pericarditis and frequency of hospitalisation in adults, but was associated with an increased risk of malignancy in patients with HIV<sup>41</sup>. No similar study in children exists. Surgical resection of the pericardium is indicated in patients with persistent constrictive symptoms following anti-TB chemotherapy<sup>37</sup>.

## Conclusions

The burden of illness associated with acquired cardiac disease in children in LMIC is significant and may be equivalent to that of congenital heart disease. Rheumatic heart disease, endomyocardial fibrosis, cardiomyopathy (including HIV cardiomyopathy) and TB are the most important causes. All are associated with poverty with the neediest children having the least access to care. The associated mortality and morbidity is high. **While detailed analysis of the cost burden of and funding for these diseases is beyond the scope of this review there is a clear disparity between the burden of disease and current research.** There is an urgent need to improve cardiac care in LMIC, particularly in sub-Saharan Africa and parts of South-East Asia where the burden is highest.

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#### Captions for figures

**Figure 1:** Parasternal long axis view echocardiogram demonstrating dilated left atrium, and 'hockey stick' deformity of stenosed mitral valve seen in rheumatic heart disease (LA, Left atrium; LV, left ventricle; AV, aortic valve; AMVL, anterior mitral valve leaflet)

**Figure 2:** Subcostal 4 chamber view echocardiogram demonstrating a hugely dilated right atrium (outlined with dashed white line) and obliteration of the right ventricle in endomyocardial fibrosis (RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle)